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‘Standard THC Units’: a proposal to standardise dose across all cannabis products and methods of administration

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Abstract

Background: Cannabis products are becoming increasingly diverse, and they vary considerably in concentrations of Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD). Higher doses of THC can increase the risk of harm from cannabis, while CBD may partially offset some of these effects. Lower Risk Cannabis Use Guidelines currently lack recommendations based on quantity of use, and could be improved by implementing standard units. However, there is currently no consensus on how these should be measured or standardised across different cannabis products or methods of administration.

Argument: Existing proposals for standard cannabis units have been based on specific methods of administration (e.g. joints) and these may not capture other methods including pipes, bongs, blunts, dabbing, vaporizers, vape pens, edibles and liquids. Other proposals (e.g. grams of cannabis) cannot fully account for heterogeneity in cannabis products. Similar to alcohol units, we argue that standard cannabis units should reflect the quantity of active pharmacological constituents. On the basis of experimental and ecological data, public health considerations, and existing policy we propose that a 'Standard THC Unit' should be fixed at 5 milligrams of THC for all cannabis products and methods of administration. If supported by sufficient future evidence, consumption of Standard CBD Units might offer an additional strategy for harm reduction.

Conclusions: Standard THC Units have the potential to be applied across all cannabis products and methods of administration in order to guide consumers and promote safer patterns of use.

Background

Cannabis is used by an estimated 192 million people worldwide (1). This number may rise further as new legal markets in Canada, the USA, Uruguay and elsewhere emerge (2), along with permissive stances towards cannabis in illicit markets (e.g. “cannabis social clubs” in Spain and “coffee shops” in the Netherlands (3)). Cannabis is also gaining increasing acceptance in modern medicine (4). However, there are long-standing concerns about the risks of cannabis use on mental health and cognition (5-7). For example, a relatively consistent finding is that greater levels of cannabis exposure are associated with an increased risk of adverse outcomes such as the development of cannabis use disorders (8, 9). Although there is debate about causality (10-12) the association between cannabis use and risk of psychosis strengthens in some individuals with increasing levels of cannabis exposure (13, 14). These risks could potentially be minimised by promoting safer patterns of use (15, 16).

Canada’s current evidence-based (16) Lower Risk Cannabis Use Guidelines (17) include recommendations such as: “If you use, choose low-strength products, such as those with a lower THC content or a higher ratio of CBD to THC” and “Try to limit your use as much as possible”. No recommendations are provided based on quantity of cannabis or cannabinoids used. There is currently no consensus on how cannabis use should be measured, which severely limits our ability to provide guidance on cannabis use and its consequences (6, 18-20). The National Institute on Drug Abuse (NIDA) Cannabis Policy Workgroup identified the development of standardised units of dose as its number one cannabis use research priority (21). The workgroup highlighted the importance of accounting for various cannabis products (e.g. herbal, edible, or extract), methods of administration (e.g. smoking, eating, vaping and dabbing), the extent to which people use multiple cannabis products, and that the active components of cannabis include CBD as well as THC (21).

Heterogeneity in quantities of THC and CBD in cannabis products

Cannabis products are extremely heterogeneous with regards to THC and CBD¹, which may have important consequences for their health effects (see Figure 1 and Table 1). Experimental studies of cannabis intoxication have shown that THC produces dose-dependent rewarding effects such as feeling “high” and relaxed, as well as THC dose-dependent adverse effects including psychotic-like symptoms, anxiety and memory impairment (5, 22-24). By contrast, preliminary evidence suggests

¹ Here we refer to ‘THC’ as the quantity of Δ^9 -tetrahydrocannabinol + $0.877 \times \Delta^9$ -tetrahydrocannabinolic acid, and ‘CBD’ as the quantity of cannabidiol + $0.877 \times$ cannabidiolic acid

that CBD can produce acute effects that are opposite to THC across a range of cognitive tasks (e.g. verbal memory, emotional face processing, response inhibition and visual processing (25)). Co-administration of CBD may partially offset some of the acute negative effects of THC on several cognitive domains and psychopathology symptoms (e.g. verbal memory recall (26, 27), emotional face recognition (28) reward processing (29-31) and psychotic-like symptoms (25, 27)).

Some evidence suggests that long-term exposure to high THC/low CBD cannabis products is associated with increased harms. These include severity and treatment rates for cannabis use disorders (32-36), risk of developing psychosis (37, 38) and relapse following a first episode of psychosis (39). Long-term exposure to CBD, evidenced by toxicological analysis of hair samples, was associated with reduced psychotic-like symptoms (40, 41) and protection from hippocampus volume loss (42, 43).

Not all experimental studies have reported protective effects of CBD (44) and some indicate it may potentiate certain effects of THC (45, 46). Moreover, exposure to CBD in observational studies may be confounded by other factors, such as lower levels of THC in varieties of cannabis that produce high levels of CBD (47). Therefore, evidence into the potential role of CBD as a harm reduction strategy is still progressing, and further evidence is needed to establish how different doses of CBD might influence the effects of THC (15). Additionally, there may be a role of other cannabinoids such as delta-9-tetrahydrocannabinol (THC) (48) and terpenoids such as limonene, myrcene, α -pinene and linalool (49) in moderating the effects of THC.

Heterogeneity in methods of administration of cannabis products

Cannabis products and methods of administration vary widely and are continuing to diversify (50). These include joints, pipes, bongs, blunts, vaporizers, edibles, liquids and others (Table 2). Methods of cannabis use vary within and across countries. For example, a multinational study (51) found that in Canada, joints were the most popular method of use (43%), followed by bongs, pipes and vaporizers (20%, 19% and 13% respectively). In Australia joints were also the preferred route (52%), followed by bongs, pipes and vaporizers (25%, 12% and 6% respectively), while in the United States the most common method was pipes (48%) followed by bongs, joints and vaporizers (19%, 14% and 11% respectively) (51). Dabbing (a method specifically used for cannabis concentrates) has become relatively widely used in new legal markets in the United States, with concentrates representing approximately 12% of all sales in Washington State (52). Edible and liquid cannabis consumption

has also risen in legal markets, representing approximately 10% of sales in Washington State (52). Distinct routes of cannabis use are associated with differences in the duration and the intensity of intoxication. The absorption of cannabinoids is more variable and slow after oral administration than for inhaled administration, which limits the ability to titrate effects based on blood cannabinoid levels (53). Overall, the high and increasing heterogeneity in methods of administration, dosage and related intoxication effects will continue to present challenges for the development of standardised guidelines that outline practical recommendations for safer patterns of use.

Previous arguments for standard cannabis units

We are not the first to discuss the concept of standard cannabis units (Table 3). Existing proposals have been based on the concept of ‘Standard Joints’ (54, 55), grams (56) and multiple types of administration (55, 57). A key study in Barcelona (54) tested the contents of peoples’ joints and equated the ‘Standard Joint Unit’ to the quantity of THC, price, and weight of cannabis from these joints. CBD was found in joints containing cannabis resin but not herbal cannabis, and was not included in the Standard Joint Unit. Advantages of this approach include its reference to a commonly used method of administration in Europe (51) which may be easily applied in research and clinical settings, and validation against problematic use (58). However, the Standard Joint Unit does not capture other methods of use. Additionally, the extent to which it reflects a standardised dose may be influenced by regional and individual variation in joints (59, 60) and changes in THC concentrations in cannabis over time (61, 62).

Grams of cannabis have been proposed as a standardised measure of quantity (56) but these do not account for variation in THC. For example, based on information from the UK in 2015/2016 (Table 1) a typical gram of cannabis concentrate might contain 26 times more THC than a typical gram of outdoor-grown herbal cannabis (780 milligrams THC compared to 30 milligrams THC). Similarly, a litre of vodka (40% alcohol by volume) would not be considered equivalent to a litre of beer (5% alcohol by volume), as it contains 8 times more alcohol (320 grams compared to 40 grams) and therefore carries an increased risk of harm.

A recent standard cannabis unit proposal addresses both THC and CBD by quantifying their relative ratio (63). Hindocha, Norberg and Tomko classified cannabis into three THC/CBD types: high THC/low CBD (.25g = 1 unit), equal THC/CBD (.5g = 1 unit), or low THC/high CBD (.75g = 1 unit) (63). However, these fixed THC:CBD ratios may not be sensitive to the varying levels of THC and

CBD found in cannabis products. For example, cannabis concentrates and outdoor-grown herbal cannabis in the UK both contain a high level of THC relative to CBD. Therefore, a gram of each of these might be considered equal, despite concentrates containing ~26 times more THC than outdoor-grown herbal cannabis.

The measurement of standard cannabis units is hindered by variation in cannabis products, their THC and CBD content, and different methods of administration. Alcohol research has faced similar issues during the development of standard alcohol units, as there is considerable heterogeneity in the types of drink consumed and the amount of alcohol they contain. Therefore, alcohol units may provide a useful framework to inform the development of objective, standardised cannabis units. Alcohol units are defined by the number of grams of alcohol (e.g. in the UK, 1 unit = 8g alcohol). Although the size of an alcohol unit varies across different countries, the use of a common metric (i.e. grams of alcohol) has allowed standard alcohol units to be applied across a wide range of alcohol products.

A new proposal for Standard THC Units

We argue that for cannabis, as for alcohol, standard units should be based on the quantity of active pharmacological products. The primary psychoactive constituent of cannabis is THC. Therefore, standardised doses of THC should form the basis of ‘Standard THC Units’ rather than other proxies of cannabis exposure (e.g. grams, joints). It is important to emphasise that dose (milligrams of THC) is different from concentration (% of THC) and the former should be used to inform Standard THC Units. This information could help to guide consumers on the number of standard doses each product contains at the point of sale (Figure 2). Evidence from Canadian respondents suggests that labels listing the number of doses on edible products were more effective at conveying information than those listing THC milligrams alone (64). As with other information on product labels, this information should be as accurate as possible while accounting for variation within a product. Qualitative data from the US suggests that serving size statements on edible products were considered useful as a “baseline” for how much that product might affect the user (65). It was also reported that serving size suggestions would be easier to comprehend if they were made equivalent to the number of “hits” on a joint rather than simply listing the number of milligrams (65). This suggests that there may be value in the concept of a Standard THC Unit and applying it to multiple cannabis products. Labelling of Standard THC Units could be incorporated into existing Lower Risk Cannabis Use Guidelines (17) such that they can provide specific recommendations based on quantity of use. Standard THC Units could be used to

inform specific policies such as minimum unit pricing, which might be especially effective at reducing harmful levels of consumption on the basis of alcohol research (66).

A major challenge for Standard THC Unit implementation is understanding how they can be applied across different products and routes of administration. This is particularly important when considering inhaled and oral administration, which have not been accounted for in previous proposals for standard cannabis units (Table 3). There are important differences in bioavailability and time-concentration profile of inhaled and oral THC. Bioavailability following inhaled THC typically ranges from 10%-35% and is influenced by factors such as the number, duration and spacing of inhalations as well as side stream smoke (67). Oral administration is characterised by significant first pass metabolism in the liver, lower bioavailability (2-14%) (67), a slower onset of absorption, lower peak concentrations and longer elimination when compared to inhaled cannabis, as well as higher 11-nor-9-carboxy-THC concentrations (68). It has been proposed that 1 milligram of THC in oral form might be considered pharmacokinetically equivalent to 5.71 milligrams of THC in inhaled form (69). However, these calculations were not based on the subjective effects of THC. Such effects have a slower onset and longer duration following oral versus inhaled administration (70, 71). However, the peak level of subjective effects has been found to be comparable between these routes (Ohlsson et al., (70); infrequent users in Newmeyer et al. (71)). Peak subjective effects may be an important component of what constitutes a Standard THC Unit (i.e. the maximum level of 'stoned' or 'good drug effect'). Therefore, these findings suggest that the same sized THC unit could be applied across oral, vaporized and smoked routes of administration (71).

We acknowledge that it will not be possible to achieve complete equivalency in the subjective effects of a Standard THC Unit across different routes of administration (as with any conversion across routes). Subjective effects may be influenced by variation in cannabis use behaviours (such as smoking topography (72)) and other factors such as tolerance (71). There are also differences in the health effects of using different methods of cannabis administration (e.g. smoking being most harmful) as recommended by current Lower Risk Cannabis Use Guidelines (16). However, using the same standardised THC unit across different products could have significant advantages in terms of acceptability, feasibility and product labelling. For example, herbal cannabis can be consumed in multiple ways including smoking, vaping and eating and many others methods (Table 2). If the size of Standard THC Unit differed for each of these methods, consumers may find it difficult to understand and estimate their unit consumption, especially if they use cannabis in a variety of ways. Labelling multiple unit sizes on a single package might create complex labels that are difficult for consumers to comprehend. This contrasts with the principle that labelling on cannabis products should be clear and

require minimal numeracy to understand (73). Therefore, labelling each cannabis product with a fixed number of Standard THC Units – which apply to all methods of use – could allow standard units to be easily implemented and better understood by consumers.

Another major challenge is establishing how many milligrams of THC should form one Standard THC Unit. Experimental studies have shown that inhaled and oral doses of THC ranging from approximately 2 to 8 milligrams can have intoxicating effects without producing severe adverse responses among infrequent users (22, 74-76). Given that frequent cannabis users can develop tolerance to the effects of THC (77) they may consume higher doses during typical use. However, 8 milligrams vaporized THC was found to produce robust subjective, cognitive and psychotomimetic effects in daily cannabis users (28, 44). This approximate dose range (2 to 8 milligrams) is supported by ecological data from a study in Barcelona (54) which estimated that a Standard Joint Unit should contain 7 milligrams of THC, on the basis of analysis of joints containing herbal cannabis or cannabis resin.

From a public health perspective, it may be considered advantageous to choose a standard THC unit that is lower than the average level of consumption (73). This could encourage people to consume less THC, as reducing the serving size of an alcoholic drink has been found to lower alcohol consumption both in experimental and real-world settings (78). A low dose could also reduce the chances of an excessive and/or unpleasant response to a single THC unit in naïve volunteers. For example, in a study administering 10 milligrams of oral THC people to people with minimal exposure (less than 15 lifetime occasions of use), 33% of the sample experienced a severe reaction such as paranoia (79). Another study of volunteers reporting no cannabis use in the past month found that 12% of the sample vomited after receiving an inhaled dose of 25mg THC (24).

The risk of unintentional or excessive dosing is especially high for edible products, due to the slow onset of effects which limits ability to titrate effects. A study in Colorado found that ingestion was responsible for 74% of all paediatric regional poison centre admissions for cannabis (80). At the time of writing, the maximum quantity of THC that can be sold in a single serving of edible is 5 milligrams in Alaska and Oregon and 10 milligrams in Colorado and Washington (81). Regulations for Canada include a limit of 10 milligrams THC for edibles (per package) and 10 milligrams THC for ingested extracts (per capsule or dispensed amount) (82). On the basis of experimental and ecological data, public health considerations, and existing policy we propose that a Standard THC Unit should be fixed at 5 milligrams of THC for all cannabis products and methods of administration. In terms of edible products, this would allow the same unit size to be applied across different regions within current legislation (half of the maximum serving size in Colorado,

Washington and Canada; the maximum serving size in Alaska and Oregon). The same 5 milligram THC unit could be applied to other products (Figure 1) including pre-rolled joints (Figure 2) to guide consumers on recommended dosage. We argue that a Standard THC Unit of 5 milligrams has the potential to be acceptable as meaningful standard dose, while being low enough to minimise the risk of adverse effects after consuming a single unit. Standard THC Units could be incorporated into Lower Risk Cannabis Use Guidelines (17) to permit quantitative recommendations for safer use.

Remaining challenges

Accounting for CBD may also be important as varying levels of CBD are present in cannabis and may influence its health effects (15). Canada's Lower Risk Cannabis Use Guidelines currently refer to CBD in terms of the CBD:THC ratio (17). However, the evidence for CBD protecting against THC harms is preliminary at present and further research is needed strengthen the evidence and identify dose-response effects (15). If supported by adequate evidence, consumption of CBD units might be recommended in future as a strategy to mitigate the harms of THC unit consumption. Such guidelines might be considered acceptable to people who use cannabis if CBD units could mitigate THC harms without compromising the 'high' they seek, as suggested by some research (15). A recent survey of people residing in US states where recreational cannabis use is legally sold found that CBD content was consistently rated as the one of the most attractive attributes of cannabis products (83). Evaluating the health impact of CBD in cannabis should be a priority given its significant interest to consumers.

Introducing Standard THC Units to public health guidelines may not be feasible in jurisdictions where cannabis use is prohibited. Illicit markets can also create barriers for research on standard units, such as participant recruitment, drug administration and collection of samples. However, if a consensus is reached on which metrics should be used to define Standard THC Units in legal markets, these "ideal criteria" could be used to update and harmonise international research methodology and clinical tools. Moving towards the quantification of active pharmacological products (THC and CBD) could improve our understanding of cannabis use and its consequences. Some researchers are already using milligrams of THC as a metric to estimate long-term THC exposure (84). Dosage of THC and CBD in milligrams can be estimated by combining information on the (i) quantity of cannabis product used, (ii) the type of product used, and (iii) its estimated THC and CBD concentration. Precision may be increased by asking people to physically estimate the amount of cannabis they use with cannabis material (85) or a substitute (85-87). The increasing number of studies quantifying THC and CBD

concentrations in illicit cannabis markets (61, 62, 88-94) and the use of pictorial aids (Figure 1) during substance use assessments (95, 96) may help to improve estimation of THC and CBD exposure in jurisdictions where cannabis use is illegal.

Conclusion

Standardising dosage using fixed quantities of THC could allow the same units to be applied across different cannabis products and routes of administration. Multidisciplinary debates in the international community of researchers, policy makers, clinicians and people who use cannabis will be instrumental for gaining consensus on standard units and their inclusion in lower risk guidelines.

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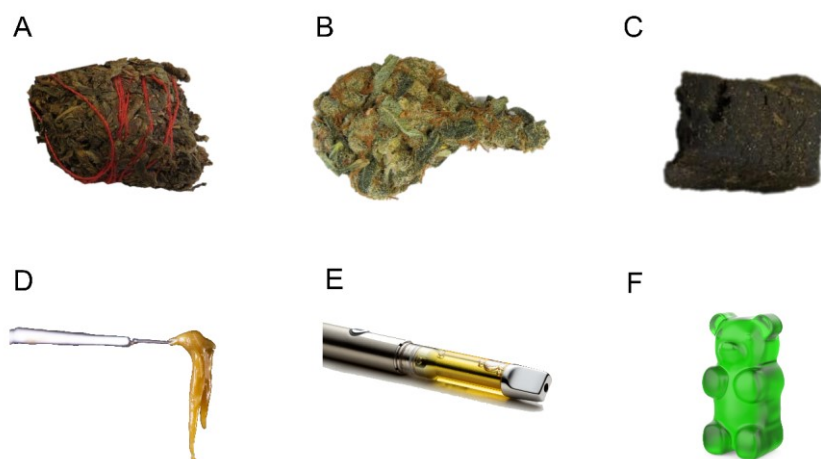


Figure 1: Heterogeneity in cannabis products: (A) Outdoor-grown herbal cannabis or 'imported herbal cannabis'; (B) Indoor-grown herbal cannabis or 'sinsemilla'; (C) Cannabis resin or 'hashish'; (D) Cannabis concentrates used for 'dabbing'; (E) Vape pen containing cannabinoids; (F) Edible gummy bear containing cannabinoids.

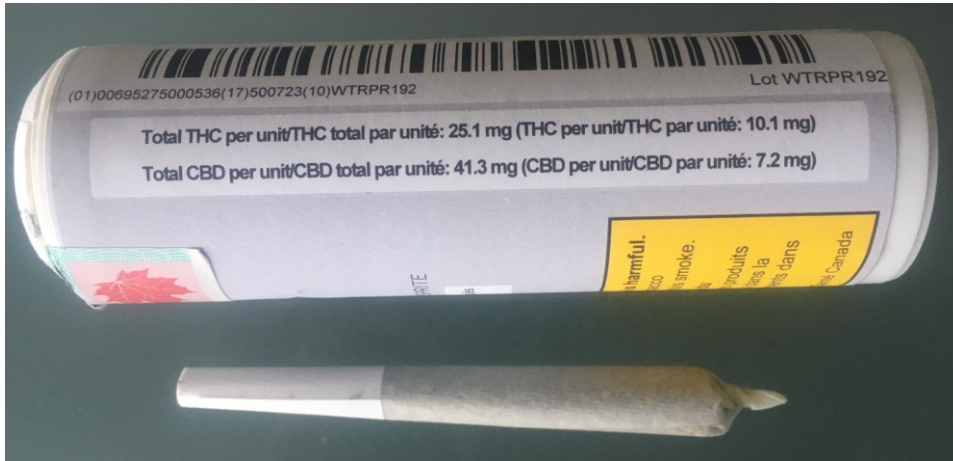


Figure 2: A package containing pre-rolled cannabis joints sold in Canada. Labels include the total quantity of THC (25.1mg) and CBD (41.3mg) per joint. No information is provided on the number of standard doses each joint contains. In order to guide consumers, labels could include additional information such as “Each unit [joint] contains five standard doses of THC”.

Table 1: Heterogeneity in typical concentrations of Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) across cannabis products and countries

Country, year	Reference	Outdoor-grown herbal	Indoor-grown herbal	Resin	Concentrates
USA, 2017	(61)	9% THC, <1% CBD	18% THC, <1% CBD	46% THC, <1% CBD	56% THC, <1% CBD
Australia, 2010-12	(88)	15% THC, <1% CBD	19% THC, <1% CBD	-	-
UK, 2015-16	(92)	3% THC, <1% CBD	14% THC, <1% CBD	6% THC, 2% CBD	78% THC, <1% CBD
Netherlands, 2015	(90)	5% THC, <1% CBD	15% THC, <1% CBD	18% THC, 8% CBD	-
France, 2016	(89)	-	-	23% THC, 4% CBD	-
Denmark, 2017	(94)	-	-	23% THC, 6% CBD	-

Table 2: Heterogeneity in methods of administration of cannabis products

Method	Route	Combined with tobacco
Joint	Inhaled, combusted	Yes/No
Pipe	Inhaled, combusted	Yes/No
Blunt	Inhaled, combusted	Yes
Bong	Inhaled, combusted	Yes/No
Dabbing	Inhaled, combusted	Yes/No
Vaporizer	Inhaled, vaporized	Yes/No
Vape pen	Inhaled, vaporized	Yes/No
Edible	Oral	No
Liquid	Oral	No

Table 3: Existing proposals for standard cannabis units/standardised measures of quantity

First author, year	Reference	Standard cannabis unit	Description	Strengths: accounts for	Limitations: does not account for
Wetherill, 2016	(56)	Gram Years	Number of daily grams consumed, multiplied by years of cannabis use	Some different methods of administration	Variation in quantities of THC and CBD
Casajuaana-Kögel, 2017	(54)	Standard Joint Unit	1 unit = 1 joint, <i>or</i> .25 grams cannabis, <i>or</i> 7 milligrams THC, <i>or</i> 1 Euro.	The most common method of administration in Europe	Variation in quantities of THC and CBD and other methods of administration
Ziesser, 2012	(55)	Standard Joint	1 standard joint = 0.5 grams cannabis, 10 puffs <i>or</i> 5 bong hits, <i>or</i> 5 pipe hits	Some different administration methods and/or number of puffs	Variation in quantities of THC and CBD and other methods of administration
Norberg, 2012	(57)	Cannabis Unit	1 unit = 0.25 grams cannabis, <i>or</i> 1 paper joint <i>or</i> 1 blunt, <i>or</i> 2 skinny paper joint/blunt, <i>or</i> 3 cones/water pipes/bongs/bucket bongs	Some different sizes of joint and methods of administration	Variation in quantities of THC and CBD and other methods of administration
Hindocha, 2017	(63)	THC/CBD ratios	High THC & low CBD (e.g. 1 unit = .25 gram) Equal THC & CBD (e.g. 1 unit = .50 gram) High CBD & low THC (e.g. 1 unit = .75 gram)	Some variation in THC/CBD ratios	Variation in quantities of THC and CBD